

Diagnosis and Treatment of Glaucoma

A Review of Recent Developments

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PROBABLY the most important development of help in the diagnosis of glaucoma in the past several years is Grant's tonography.⁴ It has contributed a great deal to the understanding of the mechanism of the various types of glaucoma and will undoubtedly contribute still more.

Tonography is a method of measuring the resistance of the eye to the outflow of intraocular fluid. It also measures indirectly the rate of production of aqueous. The test is simple to do and consists in measuring the drop in ocular tension that occurs when an electronic tonometer is allowed to rest on the eye for four or five minutes. From the measurement obtained the loss in volume of the eye is calculated and the result is expressed as the facility of aqueous outflow in cubic millimeters of aqueous per minute per millimeter (mercury) of increase in intraocular pressure that is produced by the tonometer. An electric tonometer is required because the difficulty of holding an ordinary tonometer steady for the time of the test and because the meter is more easily read than the dial of the regular tonometer. Also the electronic tonometer may be connected to a recording galvanometer so that continuous recordings may be made of the tension. If a galvanometer is not used, readings are taken every 30 seconds and the average reduction in tension calculated.

The average facility of aqueous outflow for normal eyes is about 0.22* with a range of 0.10 to 0.5. For eyes with chronic open angle glaucoma the average is about 0.10 with a spread of 0.01 to 0.15. Thus there is an overlapping zone of 0.10 to 0.15 that includes the lower range of normal and also early chronic glaucoma. Even so, however, the results of tonography may be of great assistance in confirming the diagnosis in doubtful cases. It is also valuable for following the progress of glaucoma during treatment with miotics and after operation. It is perhaps a better indication of the status of the disease in an eye than is the tension.

Of other provocative tests for the diagnosis of chronic open angle glaucoma the one which has

• Tonography is helpful in the diagnosis of doubtful cases of chronic simple glaucoma. It also gives a good indication of the status of the disease in a given eye.

The most useful miotic in the treatment of glaucoma is still pilocarpine. Carbachol is more potent but must be used in an anhydrous base ointment or in a solution of a wetting agent. DFP (diisopropyl fluorophosphate) produces undesirable side effects because of the hyperactivity of the ciliary body and iris sphincter which it causes. These can be partly overcome by using pilocarpine first. Diamox is a carbonic anhydrase inhibitor that is effective when given orally. In many cases it produces at least a temporary lowering of tension in glaucomatous eyes, apparently by reducing the secretion of intraocular fluid. Its ultimate value in glaucoma remains to be seen.

The cyclodiathermy operation which has been modified somewhat by Weekers has had a recent increase in use but the long-term results have been somewhat disappointing.

The importance of early operation in narrow angle glaucoma is becoming more and more apparent. Following iridectomy the wound should be tightly sutured to insure the prompt reformation of the anterior chamber.

stood the test of time best is the water drinking test.[†] Recent articles have confirmed this and have shown that other tests such as the lability test and the caffeine test are uncertain.

There are a number of subjects that should be included in a discussion of the treatment of glaucoma. Swan⁷ recently reviewed the rationale for the proper use of the miotics. Pilocarpine is still the most useful drug for the treatment of glaucoma of chronic type because it is stable in aqueous solutions, it penetrates the cornea consistently and it seldom causes allergic reactions. It acts by directly stimulating the smooth muscle cells of the iris

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*Cubic mm. of aqueous per minute per mm. of mercury increased intraocular pressure.

†The patient drinks 1000 cc. of water within 5 minutes after having had tension measured. The tension is then measured three or four times at 20-minute intervals. A rise of 6 mm. of mercury or more is considered "positive." The patient should have no food or liquids for 5 hours before the test.

sphincter and ciliary body. Thus the reactivity of the muscles to nervous stimuli is reduced and the annoying symptoms of ciliary spasm are much milder than after the use of cholinesterase-inhibiting miotics such as eserine or diisopropyl fluorophosphate (DFP). As it is possible to get the full effect from pilocarpine in a 3 or 4 per cent solution, stronger solutions are unnecessary.

Carbachol is much more potent than pilocarpine but is so hydrophilic that it will not penetrate the corneal epithelium from an aqueous solution. It must be given in an anhydrous base ointment or in a solution of a wetting agent such as Zephiran. Gentle massage of the cornea, through the lids, enhances absorption. However, if the epithelium be damaged either by tonometry or topical anesthesia alone, enough carbachol may be absorbed to cause severe generalized reactions including abrupt fall in blood pressure.

Eserine and DFP act by inhibiting cholinesterase so that the acetylcholine produced by nervous stimulation can have a prolonged action on the muscle cells. The resulting hyperreactivity of the muscles causes painful spasms of the iris and ciliary body. These symptoms may be reduced by administering pilocarpine before using DFP. The reactivity of the muscles is reduced by the pilocarpine so that DFP is tolerated better. The pilocarpine can then be gradually reduced.

DFP is very unstable in the presence of water and this has made its use in weaker concentrations such as 0.01 per cent somewhat uncertain. If the bottle is left open in a moist atmosphere or if the dropper is permitted to touch the lids during instillation, the resulting contamination causes a rapid loss of potency of the drug.

DFP is definitely contraindicated in narrow angle glaucoma. Numerous cases of acute attacks of glaucoma induced by DFP have been reported. Its best place is in the treatment of aphakic glaucoma where ciliary spasm is not annoying and the angle is wide.

CARBONIC ANHYDRASE INHIBITORS

Perhaps the most promising development of the last few years in the treatment of glaucoma is the use of carbonic anhydrase inhibitors. The first of these is acetazoleamide (Diamox) on which Becker² recently reported. Carbonic anhydrase was discovered in the blood in 1932. It is an enzyme that catalyzes the reversible reaction of water plus carbon dioxide to give carbonic acid. In 1940 the sulfonamides were found to be inhibitors of carbonic anhydrase. In 1950 Diamox, which is one of the sulfonamides, was brought out. It has been used since that time by internists as a diuretic. It produces diuresis by interfering with the reabsorption of bicarbonate by the renal tubules and the bicar-

bonate that passes out of the kidney carries with it a certain amount of water. Besides the diuretic effect, the loss of bicarbonate tends to bring about acidosis.

Since Kinsey⁶ found a great excess of bicarbonate in the posterior chamber of the rabbit eye, it was felt that carbonic anhydrase might play a role in the secretion of the aqueous. Therefore a substance that inhibits the action of carbonic anhydrase might be expected to cut down the production of aqueous and lower the intraocular pressure.

Diamox is given by mouth and relatively little toxic effect has been noted even when it was given for long periods of time in congestive heart failure. It has been found to lower the tension in a high percentage of normal as well as glaucomatous eyes. It had some effect in all but two or three per cent of a total of about 250 cases reported upon at the Wilmer Resident's Meeting at Johns Hopkins. Whereas it is best given in single doses every day or two when it is used as a diuretic, it has been found to be more effective on the eye when it is administered in divided doses several times a day. The maximum recommended dose for this purpose is 250 mg. every four hours. Diabetes and kidney disease are contraindications. In some patients it takes as long as three days for the tension-lowering effect of Diamox to take place. Ammonium chloride has been given to patients who have not responded to Diamox alone and this has increased the action of Diamox, apparently by lowering the pH of the blood and producing mild acidosis. Leopold observed that giving sodium chloride at the rate of 2 gm. per day reduced the action of Diamox. The reason for this has not been explained. Lederle Laboratories recently brought out sodium Diamox, which can be given intravenously. The drug is more effective intravenously than when it is given orally, and injection may be found useful in treating patients with acute glaucoma who, because of nausea and vomiting, are unable to retain oral doses of the drug.

The action of Diamox is apparently not the result of diuresis that it brings about, for the ocular tension abates before diuresis occurs. Tonographic measurements made during the administration of Diamox have shown no change in the facility of aqueous outflow. Diamox has also been found effective in lowering the pressure when the angle of the anterior chamber was completely closed with peripheral anterior synechias. This would suggest that the decreased tension is the result of inhibition of the rate of inflow of the aqueous. This was measured recently, using Goldmann's method, and it was found that the aqueous inflow was reduced by as much as two-thirds. Friedenwald gave ascorbic acid, an activator of carbonic anhydrase, to rabbits before administering Diamox. The effect of Diamox on the intraocular pressure was appreciably diminished by the ascorbic acid, which is evidence that the tension-

lowering effect of Diamox is apparently the result directly of its inhibition of carbonic anhydrase.

Many other carbonic anhydrase inhibitors are available, some more potent than Diamox. A search is under way for one that may be effective topically. As yet none has been found.

Complications that have occurred during the administration of Diamox include numbness and tingling of the extremities, headache, dizziness, nausea and insomnia. Some of these may have been coincidental, but all disappeared promptly when the drug was discontinued or the dosage reduced. Although Diamox is a sulfonamide, no cases of agranulocytosis or aplastic anemia have been observed. The possible effect of this drug on the bone marrow must be kept in mind, however. Ocular complications have included one case of optic neuritis and one case of retinal hemorrhages following five months of administration. Since the retina normally contains carbonic anhydrase, this may turn out to be a complication to watch for.

In considering other possibilities of complications, it might be conjectured that prolonged reduction of the inflow of aqueous would interfere with the nutrition of the lens and perhaps hasten the formation of cataracts. Also the stagnation of the through-and-through flow of aqueous might conceivably increase the blockage of the trabeculum or the aqueous veins or whatever it is that causes the increased resistance to outflow that is presumably the cause of primary open angle glaucoma.

The present status of Diamox would seem to be that of a useful adjunct in acute cases before operation. It also seems to be helpful in getting patients past relatively short-lived attacks secondary to trauma or inflammation. Whether it will be feasible in the long-term treatment of chronic simple glaucoma remains to be seen.

ADVANCES IN SURGICAL TREATMENT

As to the surgical treatment of glaucoma, the operation that has received the most attention recently is cyclodiathermy. A modification of technique by Weekers⁸ brought about a revival of interest in the procedure. The old method consisted of making perhaps 50 or 60 applications of diathermy three or four millimeters back of the limbus. Each application lasted one to two seconds. The results were not as encouraging as was hoped and many ophthalmologists abandoned the operation. In Weekers' technique, the applications are fewer, longer (10 to 15 seconds) and placed farther back (six or seven millimeters). Many promising reports have been published, and some investigators have gone so far as to recommend the operation for glaucoma of all types and stages, almost to the exclusion of other surgical methods. Others have not had such good results. At

the Stanford glaucoma clinic, use of the operation in early chronic primary or secondary glaucoma has not been very successful. The author certainly would not think of using this operation for early iris block glaucoma where iridectomy has not been done and believes that it should be restricted to cases of advanced glaucoma in which other therapeutic measures have failed, and perhaps to glaucoma following occlusion of the central retinal vein or diabetic rubeosis where other operations are contraindicated.

There is apparently a narrow margin of safety between the amount of diathermy required to produce permanent normalizing of the tension and that which will cause hypotony or even phthisis. In most of the cases observed by the author the tension has returned to its original level within two or three months despite repeated operations.

The surgical treatment of narrow angle or iris block glaucoma has been the subject of considerable discussion. Not long ago Barkan¹ again emphasized the importance of early operation with peripheral iridectomy done with a tightly closed incision. This procedure, he said, insures prompt reformation of the anterior chamber and prevents development of peripheral anterior synechias. In this he agrees with Haas⁵ and Chandler.³ For cases in which peripheral anterior synechia already is present, Barkan advised cyclodialysis combined with iridectomy, whereas the procedure preferred by most workers in cases of this kind is iridencleisis. The latter operation has certain definite disadvantages in iris block glaucoma. The tendency for delayed reformation of the anterior chamber may cause more adhesions to develop in the angle. Also a malignant course may be more likely to follow. The optical results of iridencleisis are seldom perfect. It would seem that every effort should be made to cure iris block glaucoma with peripheral iridectomy alone. There is no question about the early cases or cases in which operation is done in the interval between attacks. In somewhat more advanced cases where the tension has been elevated for three or four days or perhaps as long as a week, iridectomy may be done and the wound sutured. Air may then be injected into the anterior chamber under considerable pressure, which results in backward displacement of the iris and lens. This maneuver may succeed in breaking peripheral anterior synechias if they are not too well established. Most of the air must then be permitted to escape. The one patient on whom the author used this procedure was cured of an attack of acute iris block glaucoma lasting three days with a tension in the eighties. It was the third such attack, the tension having been normal between attacks. The patient needed no miotics in a six-month period of occasional observation after operation.

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